Can immobilization of an inactive iron species switch on catalytic activity in the Suzuki reaction?

short title for running heads: Iron catalyzed Suzuki reaction?

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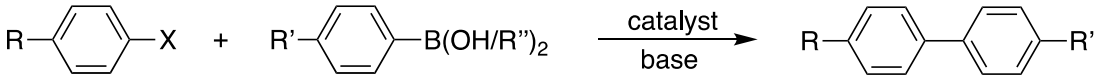
Abstract

We examined the synthetic and catalytic claims that immobilization of an Fe-PNP pincer complex (**1**) on an amine-modified graphene oxide support yields a useful heterogeneous catalyst for the Suzuki biaryl cross-coupling reaction. Complex **1** is not formed under the reported conditions, rather the iron sulfate heptahydrate starting material (melanterite) undergoes partial dehydration to give iron sulfate tetrahydrate (rozenite). Neither rozenite nor melanterite are catalytically competent.

Introduction

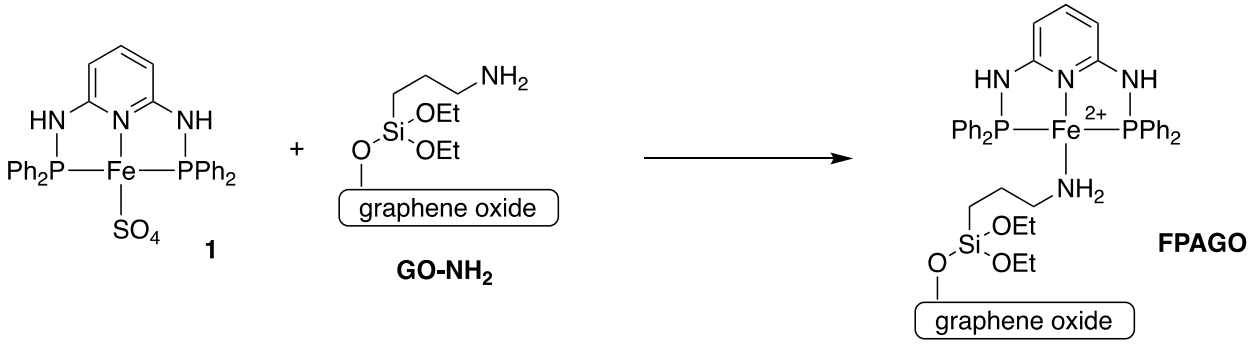
The Suzuki cross-coupling reaction, Scheme 1, is an extremely powerful method for the formation of biaryls.[1] This reaction is typically catalyzed by homogeneous complexes of palladium, but due to the expense, scarcity and toxicity of palladium,[2] there are increasing efforts to replace it with more sustainable metals, with first row transition metals attracting particular attention. Both cobalt- and iron-catalyzed Suzuki biaryl cross-coupling is showing considerable promise in the formation of biaryls,[3,4] but in these cases, the arylboron esters (or tetraorganoboronates) must be employed as the nucleophilic substrates rather than free aryl boronic acids. Early claims that aryl boronic acids could be used in iron-catalyzed Suzuki biaryl cross-coupling were subsequently retracted when the authors were unable to reproduce their results.[5,6]



Scheme 1. The Suzuki biaryl cross-coupling reaction

Apparently bucking the general trend of inactivity of iron and cobalt catalysts in the Suzuki biaryl cross-coupling of aryl boronic acids, Bhat and co-workers have reported, across a series of papers, a range of iron and cobalt catalysts for the reaction, as well as copper and nickel analogues.[7] We recently reexamined a representative range of the synthetic and catalytic claims made in five of these papers,[7a-f] most of the synthetic and all of the catalytic claims examined could not be reproduced;[3d] indeed we observed no catalytic activity with any of the catalysts examined, nor with appropriate structurally authenticated analogues. We now turn our attention to claims

made in a subsequent report by Bhat and co-workers that an Fe-PNP complex **1** can be immobilized on an amine-modified graphene oxide support, **GO-NH$_2$**, prepared by reaction of **GO** with aminopropyl triethyl siloxide (APTES) to give **FPAGO** (Scheme 2)[8] a purported catalyst for the biaryl Suzuki coupling of aryl boronic acids. Note, in the original paper, Bhat drew the iron species of **FPAGO** as a neutral amido-linked complex, however, in a personal communication he stated that the attachment is in fact an amine residue.



Scheme 2. Claimed synthesis of **FPAGO**, a PNP-Fe complex immobilized on and amine-modified graphene oxide support.

Results and Discussion

(a) On the nature of the "Fe-PNP" complex, 1.

Complex **1** does not exist, at least when the preparative route described by Bhat and co-workers is followed.[7b] This consists, *in toto*, of heating a mixture of iron(II) sulfate heptahydrate (melanterite) with the one equivalent of PNP pincer ligand in THF at reflux for 4 hours, cooling and then isolating and washing the precipitate with diethyl ether. We previously repeated this very brief synthetic protocol of complex **1** several times (performed independently by more than

one researcher), and found that it in fact gives a mixture of starting materials, in which the melanterite has undergone partial dehydration and is recovered as the precipitate from the reaction mixture.[3d] Meanwhile, the PNP ligand is recovered from the supernatant phase. The same iron-containing material can be prepared by heating melanterite in THF at reflux for 4 hours in the absence of the PNP ligand. Figure 1 shows the powder XRD we have now obtained for the supposed "PNP-Fe" complex, **1**, produced using Bhat's reported method;[7b] the material obtained on heating melanterite in THF for four hours in the absence of the PNP-ligand and a calculated powder XRD pattern derived from the reported single crystal X-ray structure of rozenite ($FeSO_4 \cdot 4H_2O$).[9] It is clear from this data, that heating melanterite in THF under Bhat's conditions, with or without the PNP-ligand, cleanly produces rozenite, not the "Fe-PNP" complex **1** claimed.

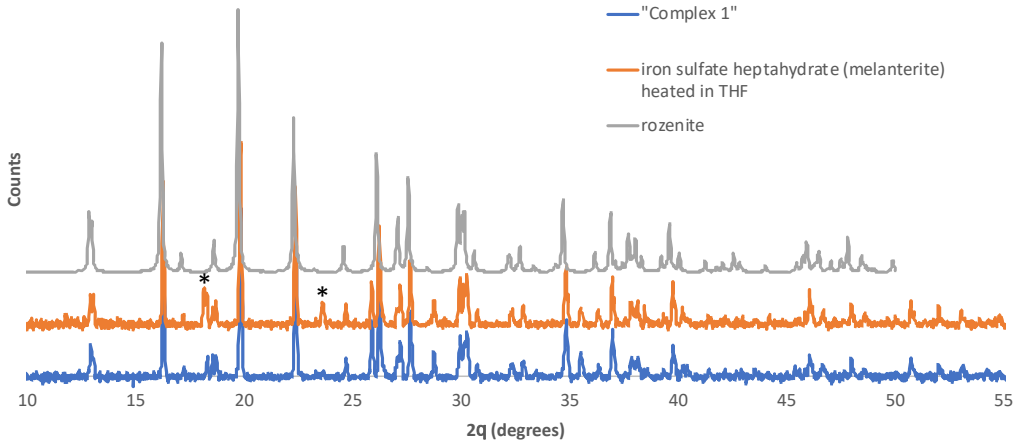
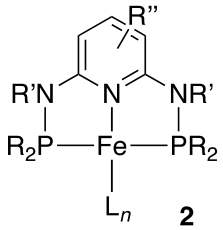


Figure 1. Powder XRD patterns for "complex **1**", as prepared by Bhat's method and iron sulfate tetrahydrate (melanterite) heated in THF in the absence of the PNP (* denotes peaks for residual melanterite) and the calculated pattern for rozenite, based on published single crystal data.[9]

This failed synthesis does not mean that PNP-Fe complexes of the general type **2** are inaccessible; on the contrary, a search of the CCDC reveals 71 have been structurally characterized,[10] ten containing the same PNP ligand as contained in the nominal complex **1**. [11-15] Clearly, the PNP ligand is not incompatible with iron, it is simply that Bhat and co-workers either overlooked or disregarded the previous examples and chose instead an iron precursor that does not react with the ligand.



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(b) On the nature of the modified graphene oxide-supported "Fe-PNP", FPAGO.

Figure 2 is the powder XRD traces reported by Bhat (reproduced with permission) for the graphene oxide (**GO**) produced according to the modified Hummer method,[16] and the iron-containing species **FPAGO**. The sharp peak at 2θ = 26° which Bhat describes as "due to the graphitic (002) plane which indicates the multilayer structure of **GO**" [8] is in fact simply the peak due to $d_{(002)}$ of unreacted graphite. Indeed, this peak, as well as the small peak at 2θ = 55° corresponding to the $d_{(004)}$ plane are readily observed in the powder XRD pattern of graphite (Figure 3) clearly indicating Bhat's samples of both graphene oxide (**GO**) and the nominally 'Fe-PCP modified' **FPAGO** are heavily contaminated with graphite. By contrast, most literature reports that contain powder XRD data for either **GO** prepared by the modified Hummer

method,[16] or **GO-NH$_2$** show little or no residual graphite, indeed the paper cited by Bhat for the preparation of **GO-NH$_2$** by Kan and co-workers shows no graphitic peaks in the powder XRD for either **GO** or the **GO-NH$_2$**.[17] The relatively low percentage of **GO** in the sample prepared by Bhat is also evidenced by the absence of a strong signal in the IR spectrum at around 1730 cm^{-1},[8] corresponding to the ν(CO) of the carboxylic acid group of **GO**.[16] When Kan functionalized **GO** with APTES to give **GO-NH$_2$**, the peak at 2θ = 11.3 Å, corresponding to the $d_{(002)}$ of layers of **GO**, was shown to weaken immensely, while the broad peak around 2θ ~ 22 Å grew,[16] a phenomenon attributed to functionalization of the oxygen groups by the APTES giving a structure closer to reduced graphene layers.[18] By contrast, an examination of Bhat's diffraction data for **FPAGO** shows little variation between the peak at 2θ = 11.3 Å and that around 22 Å, suggesting little change before and after the impure graphene oxide, heavily contaminated with graphite, was reacted with the APTES and the supposedly amine-modified variant. Taken together, Bhat's powder XRD and IR data indicate the incomplete formation of **GO** and little subsequent modification on reaction with APTES, compared with the data published by Kan on which Bhat's procedures were based.[16]

It is not possible to determine what the structure of **FPAGO** is based on Bhat's data. It is clear the **GO-NH$_2$** support is not predominantly what he claims it is, and the pincer complex **1** is not formed according to his reaction conditions, rather the melanterite precursor undergoes partial dehydration. However, does mixing the impure support with partially dehydrated iron sulfate give a covalently immobilized species? Bhat claims that the peak at 2θ = 6° (which actually appears to be closer to 2θ = 7.1°) in **FPAGO** is also present in the (unreported) powder XRD

pattern of “complex **1**”. If this peak is indeed observed in whatever unidentified phase of partially dehydrated melanterite Bhat obtained in his reaction, then its appearance in the pattern of **FPAGO** is not consistent with a covalently attached species, but instead a physical mixture. A covalently-attached species would of course have a different structure and thus a different PXRD trace.

Summarizing, the material **FPAGO** can best be described as a physical mixture of a support comprising graphite with some graphene oxide, which may contain an amount of an amine-modified graphene oxide and an unknown iron salt, one that does not contain a PNP ligand (although some of the ligand may have been carried over into the physical mixture as an unreacted impurity, depending on how assiduously the partially dehydrated iron sulfate precipitate was washed).

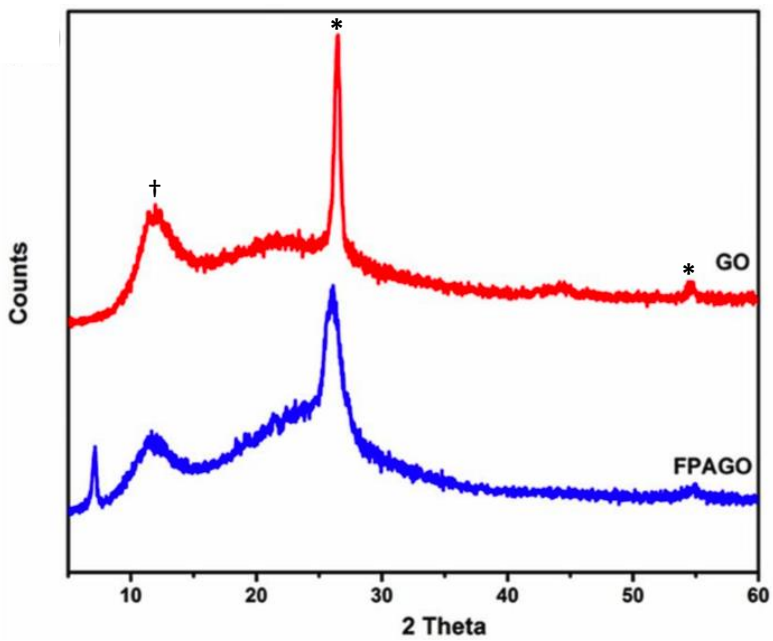


Figure 2. Bhat's powder XRD of **GO** and **FPAGO** (reproduced with permission); The * indicate peaks due to graphite, the powder XRD of a genuine sample of which is shown in Figure 3. The † indicates the peak due to $d_{(002)}$ peak of **GO**.

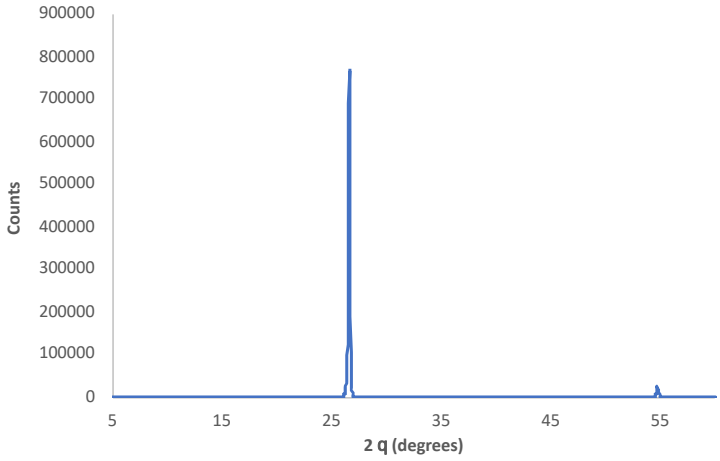


Figure 3. Powder XRD pattern of commercial graphite.

(c) On the purported catalysis

Figure 3 shows a summary of the performance reported across six papers by Bhat and co-workers of twelve very different selected catalysts in the Suzuki biaryl coupling reaction shown, with acetonitrile as solvent, employing a variety of bases. [7a-f, 8] As can be seen, with one or two minor exceptions, it appears that this reaction gives Bhat and co-workers a surprisingly consistent yield of about 80%, irrespective of the metal, the ligands or whether the catalyst is a homogeneous or heterogeneous species. We previously reinvestigated both the reported structures and the catalytic performance of a representative range of these catalysts. Our findings on the catalyst structures are very briefly summarized in Figure 3, while full details are given in ref. [3d]. Importantly, we found none of the catalytic claims made by Bhat were

substantiated. We specifically reinvestigated the catalytic reaction shown in Figure 3, using a selection of the nominal 'catalysts', under the optimal conditions in each case reported by Bhat; these are identified by a red asterisk on the plot in Figure 3: none of these reactions gave any conversion to the biaryl product on repeated attempts, conducted independently by several researchers.

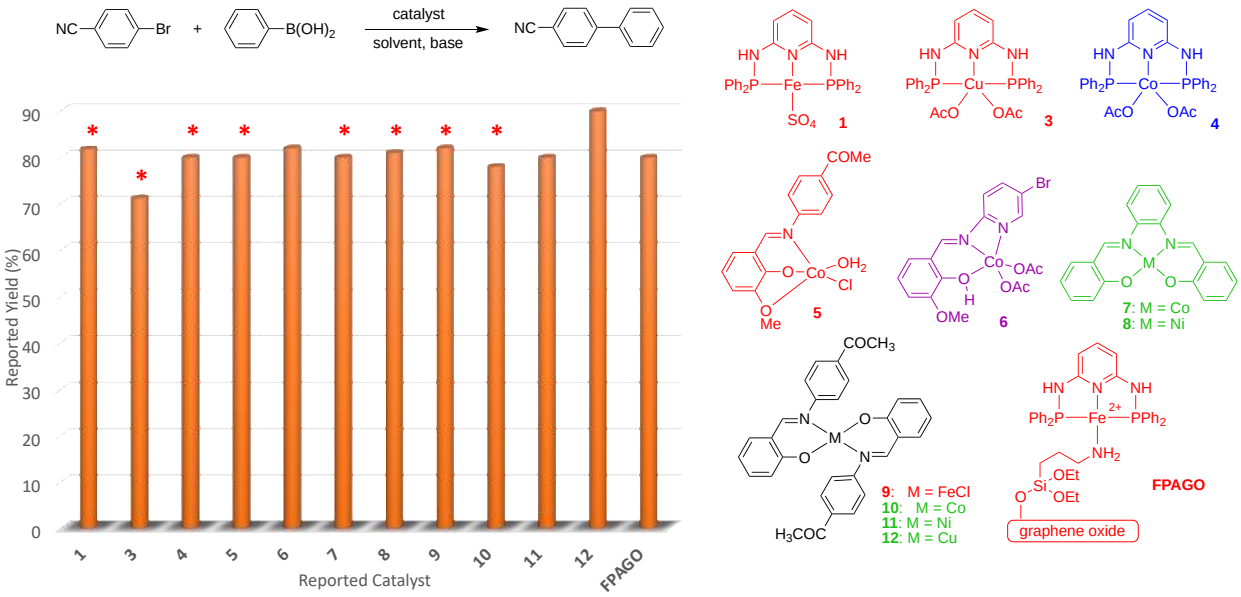
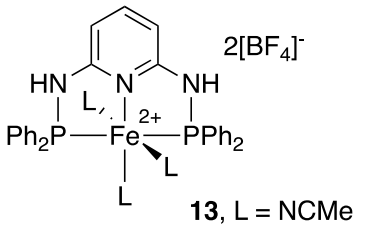


Figure 3. Catalysis of the reaction of 4-bromobenzonitrile with phenylboronic acid in acetonitrile as claimed by Bhat and co-workers using the catalysts shown. * indicates reactions we previously reinvestigated[3d] using the optimal conditions reported by Bhat; in all cases no activity was obtained. Color coding of catalyst structures: Red (**1**, **3**, **5**, **9** and **FPAGO**), demonstrated to be incorrect; purple (**6**), improbable structure with insufficient supporting data; blue (**4**), reasonably

likely to be correct structure; green (**7**, **8**, **10** – **12**), likely correct as reported (see ref. [3d] for full details).

Against this backdrop, we now discuss the feasibility of the catalytic activity reported by Bhat for **FPAGO**. As can be seen in Figure 3 this too is reported to give around 80% in the reaction. **FPAGO** is apparently produced from PNP-Fe, **1**, but as we have shown both previously[3d] and above, complex **1** does not form according to Bhat's synthesis. Instead the iron sulfate rozenite is formed. We previously showed that rozenite, formed in the presence or absence of the PNP ligand, does not catalyze the reaction shown in Scheme 2, nor does the starting iron sulfate, melanterite. In order to give Bhat's catalytic claims the fairest possible test, we had also examined the previously reported, crystallographically characterized complex **13**, a genuine example of an Fe-PNP complex, with the same pincer ligand for comparison purposes.[3d,19] We chose this complex because during catalysis in acetonitrile – a solvent that purportedly engenders good catalytic activity in Bhat's various studies – the acetonitrile should displace the sulfate ligand (note: the drawing of **1**, showing *S*-bound sulfate, as per Bhat's rendering, is, of course, not possible) giving a common catalytic intermediate, regardless of the structure of the pre-catalyst. Furthermore, if Bhat's catalytic results are to be believed, and that little or no perturbation is obtained on changing metal, ligand or phase, then minor perturbations in the coordination sphere of the pre-catalyst should have negligible effect. Complex **13** does not catalyze the Suzuki coupling shown in Figure 3.[3d] It is possible that the sulfate ion, missing from complex **13**, is in some way essential for catalysis. We had not explored this possibility previously,[3d] however we

have done so now; no activity is obtained in the Suzuki reaction outlined in Figure 3, catalyzed by complex **13** in the presence of sodium sulfate.



13, L = NCMe

We are unable to directly test the specific catalytic claims made by Bhat regarding **FPAGO**.[8] To do this fairly, we would need to be able to recreate his heterogenized 'catalyst'. But this would entail synthesizing the right amount of **GO** impurity in graphite, and then partially converting this impurity into a nominal amount of **GO-NH_2** and subsequently reacting this mixture with precisely the right amount of whichever iron sulfate phase Bhat obtained (with or without an unknown quantity of unreacted PNP ligand impurity). This is not practicable. However, given the following facts: (a) reaction of the PNP ligand with melanterite in THF under the conditions reported by Bhat gives rozenite, not complex **1**; (b) neither rozenite made in the presence or absence of PNP ligand nor melanterite catalyze the Suzuki reaction; and (c) complex **13**, a species that should form the same intermediates as the putative pre-catalyst **1** in the catalysis in acetonitrile does not catalyze the reaction in the presence or absence of sulfate, then we can conclude that whatever the true composition of **FPAGO**, it is extremely unlikely that it is an active catalyst for the Suzuki biaryl coupling reaction.

In summary, while we cannot absolutely exclude the possibility that 'immobilizing' impure iron sulfate (possibly with traces of unreacted PNP ligand) on a mixture of graphite with some GO that has undergone partial amine functionalization switches on otherwise latent catalytic activity in a Suzuki biaryl cross-coupling reaction that has never reproducibly been shown to be catalyzed by any iron complexes, it seems, to us at least, highly improbable. Accordingly, we urge both readers and potential reviewers of all Bhat's papers on Suzuki cross-coupling with first row transition metal complexes to heed Sagan's aphorism that extraordinary claims require extraordinary evidence. In the case of the claimed **FPAGO** catalyst and its putative homogeneous progenitor, this bar has very evidently not been cleared.

Experimental

General information

Acetonitrile was degassed and dried over activated molecular sieves (4 Å). Graphite was purchased from Sigma Aldrich. ^{1}H, and ^{31}P NMR spectra were recorded on a Bruker Nano 400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) referenced to the solvent residual peak. Multiplicities are abbreviated as: br (broad), s (singlet), m (multiplet). Powder X-ray diffraction data was collected on a Bruker D8 Advance with Cu-K α radiation (λ = 1.540600 Å) and a PSD LynxEye detector, in Bragg-Brentano geometry. Data was collected over a 2θ range of 5-60° with a 0.02° step size and 1 seconds per step.

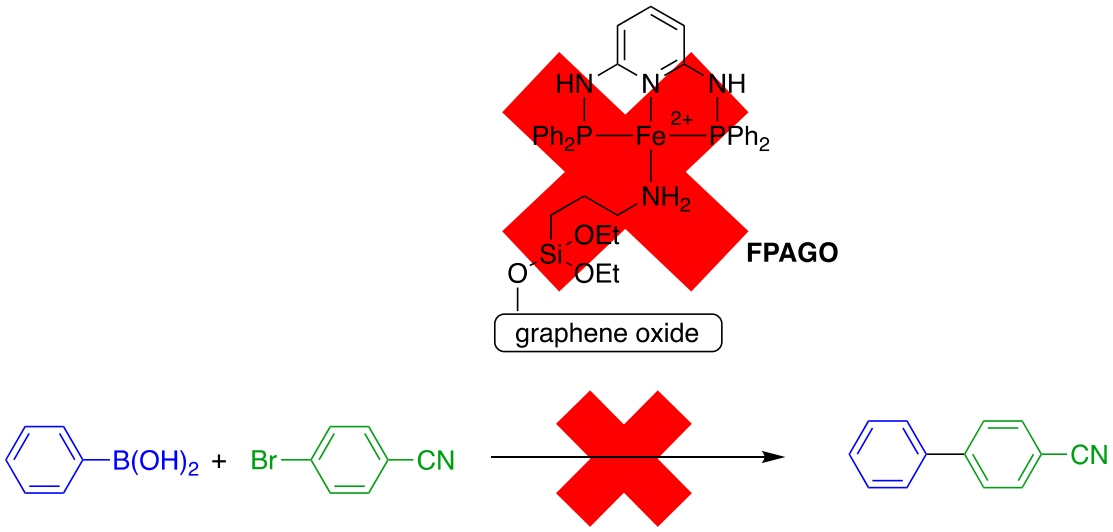
Synthesis of complex 13

Complex **13** was synthesized according to a literature method and an orange solid was obtained (90%). [19] ^{1}H NMR (400 MHz, CD_3CN) δ 8.30 (br s, 2H), 7.92-7.56 (br m, 21H), 6.65 (br s, 2H). $^{31}P\{^{1}H\}$ NMR (162 MHz, CD_3CN) δ 102.30.

Catalytic protocol

The reaction was attempted according to the procedure reported by Bhat, [7a] with the addition of Na_2SO_4. Under an atmosphere of dry nitrogen, complex **13** (0.004 mmol, 0.0033 g), phenylboronic acid (1.3 mmol, 0.1585 g), Cs_2CO_3 (2.0 mmol, 0.6516 g) and anhydrous Na_2SO_4 (1.0 mmol, 0.1420 g) were stirred in MeCN (5 mL) for 30 minutes. 4-Bromobenzonitrile (1.0 mmol, 0.1820 g) was added slowly in portions. The reaction was heated to reflux conditions and allowed to stir for 14 h. The reaction was cooled to room temperature, quenched with sat. NH_4Cl (2 mL) and the organics were extracted using CH_2Cl_2 (3 x 10 mL) and dried over anhydrous $MgSO_4$. The organic extracts were filtered and analyzed by GC-MS. The reaction was also repeated using a lower amount of anhydrous Na_2SO_4 (0.01 mmol, 0.0014 g) instead. In both cases, no 4-phenylbenzonitrile was observed by GC-MS.

Graphical Abstract:



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